THE CARBOHYDRATES OF THE URINE IN DIABETES INSIPIDUS.

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Recently Rosin and v. Alfthan reported their results from the estimation of the unfermentable carbohydrates of the urine in diabetes mellitus. They make the interesting statement that beside the well-known excretion of glucose in pathological quantities there is in this disease a marked increase in the unfermentable carbohydrates. The daily amount of the total urinary carbohydrates under normal circumstances was never, in their experience, notably more than 5 grammes, and averaged roughly about 1.6 grammes. Similar amounts have been found with normal subjects by several other workers. On the other hand, the smallest daily amount of unfermentable carbohydrate alone in fermented diabetic urine was found by Rosin and v. Alfthan to be about 9 grammes, and in some instances they demonstrated as much as 20 grammes. They conclude from these results that diabetes mellitus can no longer be looked upon as a pure "glucose disease," but is rather a disturbance of carbohydrate metabolism in general.

The method used was precipitation of the carbohydrates by benzoyl chloride in the presence of sodium hydrate. The carbohydrates come down after prolonged shaking of the mixture as benzo-esters, and when the method is properly carried out the precipitate can be fairly readily collected on a filter, washed, dried over sulphuric acid, and weighed. Since the method was described by Baumann it has been investigated by Wedenski, v. Fodor, Roos, Lehmann, Salkowski, Baisch, and Lemaire, and it has been shown that the results obtained indicate with a very fair degree of accuracy the amount of carbohydrate in the urine, when this is small, as is the case under normal circumstances. The precipitate seems to be composed very largely of the esters formed from the carbohydrates, and although there is a slight admixture of nitrogenous matter and salts, and perhaps the esters are in small part not the product of carbohydrates, the error is not sufficient to interfere with the use of the method as an index of variations in the carbohydrate excretion.

Several points in the papers by Rosin and v. Alfthan arrest one's attention. In the first place, they note that it is of interest to learn whether the unfermentable carbohydrates are still excreted in large amounts in diabetes mellitus when the glucose excretion has disappeared under the influence of diet. This might prove to be a point of serious importance in prognosis. Further, v. Alfthan states that in one case of diabetes insipidus which he had under observation, but which at the time of his report had not been completely investigated, the carbohydrates seemed to be increased. If an increase could be shown in a considerable percentage of cases of diabetes insipidus it might indicate an interesting relation between this affection and diabetes mellitus. These suggestions led me to make a series of estimations of the esters formed by this method in the urine of a patient in Dr. Stengel's wards at the University Hospital.

The man, who was an intelligent clerk, aged twenty-seven years, was admitted January 7, 1901, with a history of rather sudden onset, in June, 1900, of polyuria and excessive thirst. This had persisted and had been accompanied by decided loss of weight—about thirty pounds. He stated that his physician had examined his urine repeatedly and had told him that he had diabetes, but he had had no notable increase of appetite and no other symptoms that would strongly indicate the existence of diabetes mellitus, and the urine when he came to the hospital contained no sugar and no acetone, or diacetic acid; albumin and casts were likewise absent. The daily amount of urine was, however, above 4000 c.c., and he had excessive thirst. At the time of admission it was readily discovered that the man was in the early stages of typhoid fever, and he went through a typical mild course of this disease. It seemed possible from the history that he gave that he actually had diabetes mellitus and that the glycosuria had disappeared under the influence of the typhoidal infection. It was with the thought in mind that under such circumstances the benzoyl chloride method might prove to have actual diagnostic value that the estimation of the esters was first undertaken, for a persistent excess in their amount may perhaps be present under such conditions, and if present would probably be a valuable indication of the actual existence of diabetes mellitus in the temporary absence of glycosuria. This point is certainly worthy of investigation, as is the amount of esters found by this method in the urine of those persons who are constantly ready subjects of alimentary glycosuria, those who have hereditary predisposition to diabetes mellitus or other metabolic disturbance, or those who for any other reason are suspected of being ready subjects of diabetes mellitus. The further course of the case under discussion has demonstrated that it is not diabetes mellitus, but, as seemed highly probable from the beginning, diabetes insipidus. Sugar has always been absent from the urine, and the man has had no symptoms excepting undue thirst and polyuria, barring those of typhoid fever. The daily urine now averages about 4500 c.c.

The results obtained in estimating the esters may then be considered solely in their relation with diabetes insipidus. I was unable for a number of reasons to carry out the work until the man had practically begun his convalescence from typhoid fever; the diuresis had been a little reduced by this time through limitation of his fluids so far as was compatible with comfort.

The conclusion that may at once be drawn from the figures in the following table is that the carbohydrates were not increased; the figures obtained by control estimations of the esters and by coincident nitrogen estimations for a part of the time (Kjeldahl method) are given for reasons which will be noted later:

Date.	Amount of urine in c.cm.	Esters in gms.	Nitrogen in gms.
February 7	3670	2.752	. . . .
" 8	3820	6.494 6.229	. . . .
" 11	3280	2.427 2.099	. . . .
" 12	3370	2.830 2.897	. . . .
" 13	3450	2.484 2.691	14.076
" 14	4050	2.277 2.754	13 923
" 15	4100	1.517 1.413	12.628
" 16	2120	1.611 1.484	8.814
" 18	3400	1.666 1.768	15 803
" 19	1800	1.512 1.368	11.551
" 20	1840	1.325 1.288	9.991

The figures of February 8th are, to be sure, somewhat abnormally high, but they are so wholly at variance with all the other results in this case that I am inclined to think that there was an error in technique. The close correspondence of the control results speaks against this (the two estimations were carried out separately from the beginning), but even though the figures be correct the result is such an isolated one that it deserves no special comment, and all the other figures are wholly within the normal range. So far, then, as this case goes the results speak against the probability of any marked increase in the urinary carbohydrates in diabetes insipidus. One would certainly be inclined to anticipate this from the beginning, as no other similar relation between this disease and diabetes mellitus has been demonstrated. I should not be surprised, however, were a rather high excretion of urinary carbohydrates shown to be present in many cases of diabetes insipidus as a result of the excessive diuresis alone, not as an indication of disturbed carbohydrate metabolism. An increase of the urinary carbohydrates in this disease, unless very marked, could scarcely be looked upon as evidence of any primary disturbance of the metabolism of carbohydrates, for it is well known that flushing the system with large quantities of water will cause a marked increase of the nitrogen output, and I have shown that this persists over a considerable period, and perhaps constantly so long as the excessive amounts of water are taken; a positive nitrogen balance may even be converted into a nitrogen loss in this way. Similar results were obtained by Ter Gregorianz and Karchagin in normal subjects in nitrogen equilibrium, and by Matzkevich and Grusdiev in subjects of typhoid fever who showed a negative nitrogen balance. It is wholly probable, then, that the constant flushing in diabetes insipidus may carry off an abnormally large amount of carbohydrates in the urine, and that a portion of the increase in diabetes mellitus which was observed by Rosin and v. Alfthan may be due to the same cause, though this alone could not produce the very marked change seen in the latter affection. Another fact which would lead one to expect an increase with the free diuresis of diabetes insipidus is that actual glycosuria may be produced by some diuretics which act directly upon the kidney. That increase or decrease in the diuresis does cause an increase or reduction in the urinary carbohydrates is, I think, shown fairly definitely in the table given above. From February 15th to February 20th, inclusive, the man's fluids were reduced to as low a point as was possible without causing serious distress. The excretion of urine remained high on the 15th, though he certainly got only about 3000 c.c. of fluid in both food and drink during that day. On the 16th, 17th, 19th, and 20th the excretion was far lower than at any other period of observation. (The amount of urine on the 17th was 1780 c.c., but the esters were not estimated.) The average figures for the esters up to February 14th (excluding the result on February 8th, which is very probably incorrect) is 2.598 grammes; for the period from February 15th to February 20th, inclusive, 1.499 grammes. Hence the restriction of fluids reduced the esters to 58 per cent. of their previous amount. If the two periods be made according to the drop in the excretion of urine it is interesting to note that the average of esters for the period from February 7th to February 15th, inclusive, is 2.410 grammes, while for that from February 16th to February 20th, inclusive, is 1.502 grammes, while the average amount of urine in the same periods is 3650 c.c. and 2290 c.c. respectively. The average amount of esters in the second period is, then, 62 per cent. of the average in the first period, while the average amount of urine in the second period is 63 per cent. of that in the first period. This correspondence between the diuresis and the amount of esters, while its exactness is probably largely accidental, is too close to allow one to overlook the fact that the two bear a decided relation to each other. Diet could have played no part in this, as absolutely the only change made in the man's regimen was in the amount of water given him. Throughout the whole series of estimations he was given exactly the same food in constant quantities; the food consisted of milk, eggs, butter, bread, and sugar. The amount of carbohydrates in the urine is, therefore, evidently influenced to a very decided degree by the amount of urine passed and very probably, as suggested by Rosin and v. Alfthan, by the diet also. It is quite possible that excessive diuresis is sufficient to explain the result obtained by v. Alfthan in his case of diabetes insipidus, and it would certainly be necessary to demonstrate a very marked increase in order to show by this method even a probable relation between diabetes mellitus and diabetes insipidus so far as carbohydrate metabolism is concerned. If further investigation should show a moderate increase of esters in diabetes insipidus I should be very strongly inclined to attribute this increase wholly to the abnormal diuresis. The man whose case I report did not show any increase at the time of the investigation, but it would not surprise me if another series of estimations undertaken in the same case after six months or a year had passed demonstrated larger quantities of carbohydrates than those reported here, for the man was, as stated, convalescing from typhoid fever when these estimations were made. A marked tendency toward the laying on of tissue after severe acute diseases is demonstrated both by clinical observation and by exact determinations of the intake and outgo in such subjects. This man was increasing in weight and was evidently retaining nitrogen, as his food contained about 15 grammes of nitrogen while his excretion in the urine was notably more than 14 grammes in only one instance. It seems to me that he was very probably excreting less carbohydrates also than would be the case under ordinary circumstances. At any rate, this possibility is of sufficient interest to deserve investigation in other instances.

The nitrogen was estimated for a number of days coincidently with the esters for two reasons: To see whether there was the same relation between the amount of fluids taken and the nitrogen excretion that I have previously referred to; and to see whether there was any relation between the nitrogen excretion and the excretion of carbohydrates. The latter point was chiefly of interest because v. Alfthan stated that he thought that the unfermentable carbohydrates may be looked upon as derived from body protein or from glycogen—*i. e.*, that they are produced in the body. If they are derived from body protein their excretion should show some relation to the nitrogen excretion if the nitrogen intake is kept constant, as was practically the case with this man. In regard to the latter point the ratio of esters to urinary nitrogen was as follows: February 13th, 1 to 5.44; February 14th, 1 to 5.53; February 15th, 1 to 8.5; February 16th, 1 to 5.69; February 18th, 1 to 9.2; February 19th, 1 to 8.02; February 20th, 1 to 7.65. There was a general tendency for the nitrogen and the esters to rise and fall together, as most of the urinary solids tend to do in a general way. There was not the slightest tendency, however, toward the maintenance of any fixed ratio in the excretion of the two, and so far as such an observation goes it points against the formation of the urinary carbohydrates in this case from body protein. So complex a question cannot be settled in this off-hand manner, however, and this point in the figures is not worthy of much insistence. The question of the origin of the carbohydrates will be touched upon again at the end of this paper. The nitrogen excretion shows, in general average, the same rise and fall with increase or decrease of intake of fluids that I have previously described, and I think that it is quite thoroughly established by the observations to which I have referred and by my own earlier results that excessive water ingestion increases protein metabolism—a fact which is, as I have previously insisted, of much importance in explaining the clinical results of immoderate use of fluids.

There are one or two points concerning the benzoyl-chloride method that may be worthy of mention. In the first place, it is absolutely essential to have a good preparation of benzoyl chloride—a fact which is not sufficiently insisted upon by those who have previously discussed the method. Some of the difficulties in the use of the method described by several authors were not improbably due to the use of impure benzoyl chloride. I tried in all ways that I could devise to obtain a satisfactory precipitate with what was thought to be a perfectly satisfactory preparation, but had no success in about two weeks' work. I then secured some benzoyl chloride from another source, and afterward met with absolutely no difficulty in carrying out the method. The first specimen was undoubtedly faulty, though it was not evident in what way, and I made no serious attempt to learn what was wrong. In carrying out the method one should be careful to shake the mixture gently at first in order to avoid producing an emulsion. If shaken gently for ten minutes, or thereabouts, and then more vigorously for about twenty or twenty-five minutes, the esters precipitate extremely well and can be washed readily. I found it unnecessary to shake the mixture for "at least one hour," as recommended by a number of writers. Finally, Salkowski recommended that the mixture be shaken for a half-hour and then stood aside overnight before filtering. This is, I think, unsatisfactory. I have had good flocculent precipitates become sticky and impossible of filtration after such a procedure. The esters tend to become sticky after standing even when they have been washed and placed in a closed vessel over sulphuric acid.

The figures for control estimations were introduced into the table merely to show that absolutely exact results are not obtained by the method. It has been the general experience that control estimations are likely to show variations in results as large as 10 per cent. or more.

My results show this in most instances. Two estimations were made every day after the first, the whole process being carried out separately in each case, even in precipitating the phosphates before adding the benzoyl chloride. Exactly the same amount of urine, of benzoyl chloride, and of sodium hydrate was used in each estimation, the mixtures were shaken for the same length of time, cooled in the same manner, filtered coincidently, and each was washed just to the point where the filtrate became neutral, yet the decided variations shown were not avoided. These variations are, however, not sufficient to make the method of questionable value when used only as an index and when, as in the work herein reported, small variations have no influence upon the conclusions reached.

v. Alfthan states that his results in estimating the esters in a normal subject throughout a series of twelve days showed figures varying from 1.5 grammes to 5.1 grammes. My patient showed much more constant excretion. When taking large quantities of fluid the esters varied only between 2.099 grammes and 2.897 grammes, exclusive of the wholly erratic result on February 8th. The amount fell when the fluid was reduced, but there was only slight subsequent variation, the figures ranging only between 1.768 and 1.288. Since this man was on constant diet, and there is no statement that such was the case with v. Alfthan's (normal) subject, who showed such marked variations, it seems to me extremely probable that the amount of carbohydrates in the normal urine depends largely upon the diet, and that these carbohydrates are in large part at least derived from the food rather than formed in the body. I would say again, however, that this question is still widely open.

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